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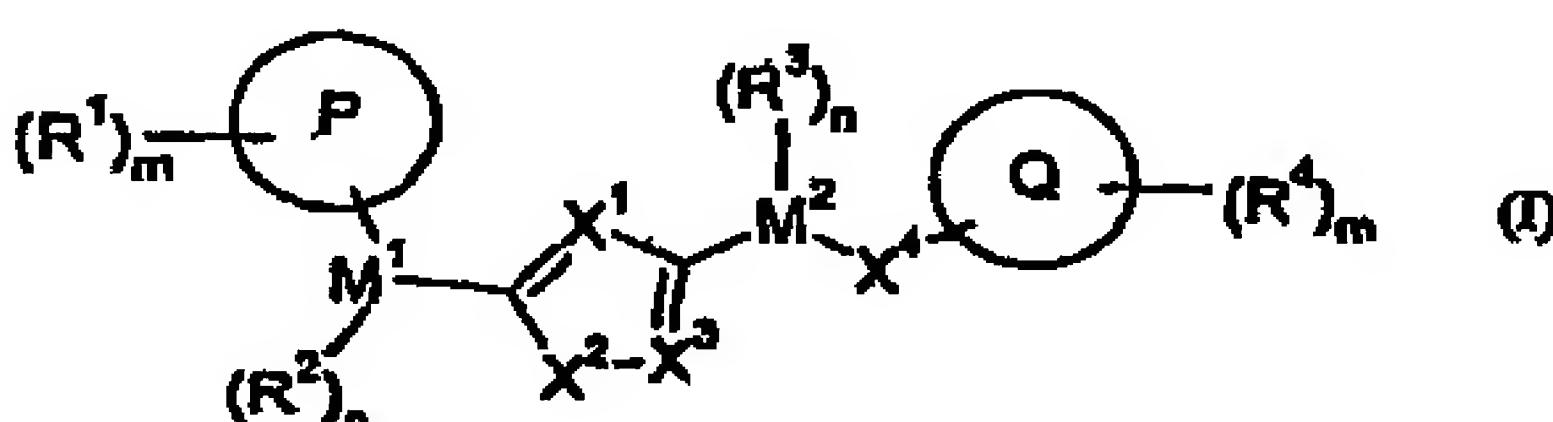
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: "1,2,4"OXADIAZOLES AS MODULATORS OF METABOTROPIC GLUTAMATE RECEPTOR-5



(57) Abstract: The present invention relates to new compounds of formula (I), a process for their preparation and new intermediates prepared therein, pharmaceutical formulations containing said compounds and to the use of said compounds in therapy. In particular, there are compounds according to the present invention that are potent and selective for the mGluR Group I receptor

and more particularly for mGluR5. Thus, it is expected that the compounds of the invention are well suited for the prevention and/or treatment of mGluR5 receptor-mediated disorders such as acute and chronic neurological and psychiatric disorders and chronic and acute pain disorders.

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INTERNATIONAL SEARCH REPORT

PCT/US 03/24846

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/12 C07D413/14 C07D417/14 A61K31/4245 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 26927 A (STORMANN THOMAS M ; DELMAR ERIC G (US); MOE SCOTT T (US); SMITH DAR) 3 June 1999 (1999-06-03) page 5, line 30 – line 34; claims 1,15,16 figure 1, compound 5 ---	1-27
X	EP 0 397 365 A (PFIZER) 14 November 1990 (1990-11-14) claims 1,14 examples ---	1-27
X	US 5 140 034 A (BAKER RAYMOND ET AL) 18 August 1992 (1992-08-18) column 1, line 5 – line 15; claim 1 column 4, line 25 – line 42 ---	1-27 -/-



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

9 December 2003

Date of mailing of the international search report

23/01/2004

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 422 369 A (BAYER AG) 17 April 1991 (1991-04-17) page 4, line 26 - line 44; claims 1,10; table 1 ---	1-17,28
X	WO 00 35913 A (AVENTIS CROPSCIENCE GMBH) 22 June 2000 (2000-06-22) page 22; claims 1,9; table 1 ---	1-24,28
X	HOLLA B S ET AL: "Synthesis and antibacterial studies of a new series of 1,2-bis(1,3,4-oxadiazol-2-yl)ethanes and 1,2-bis(4-amino-1,2,4-triazo 1-3-yl)ethanes" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 35, no. 2, February 2000 (2000-02), pages 267-271, XP004330420 ISSN: 0223-5234 compounds 4 and 5 tables I,II ---	1-24
X	GÜNEY N S ET AL: "5-Nitroimidazole derivatives as possible antibacterial and antifungal agents" IL FARMACO, vol. 54, 1999, pages 826-831, XP002264297 ROME, IT ISSN: 0014-827X tables 1,2 ---	1-24
X	MADRONERO R ET AL: "Tetrazole analogues of arylthiazolylacetic acids. Synthesis and pharmacological study" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY., vol. 9, no. 4, 1974, pages 445-448, XP009022649 EDITIONS SCIENTIFIQUE ELSEVIER, PARIS., FR ISSN: 0223-5234 scheme 1 abstract ---	1-27
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 4885431 XP002264298 5,5'-(1,2-ethanediyl)-bis'3-(m-tolyl)-1,2, 4-oxadiazole! & ORG. MASS SPECTROM. (1991), 26(11), 1017-1018, ---	1-17

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 4208871 XP002264299 & SYNTH. COMMUN. (1990), 20(12), 1811-1817,</p> <p>---</p>	1-17
P,X	<p>DATABASE CHEMCATS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002264300 Order numbers: SPB 01075, SEW 03694, BTB 02953 & "Maybridge HTS" 14 May 2003 (2003-05-14) , MAYBRIDGE PLC , TINTAGEL, CORNWALL, PL34 0HW, UK</p> <p>-----</p>	1-17

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The present application contains four separate independent compound claims of overlapping scope (see claims 1, 2, 16 and 17). The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection (Article 6 PCT). A further lack of clarity arises owing to the fact that a seemingly arbitrary selection of compounds have been disclaimed in claim 2 but not in the broader claim 1. Many of the variables in the claims are so ill-defined that it is impossible to determine the subject-matter for which protection is sought. For example, it is not clear whether the definition of X4 in claim 2 as being $C_0-C_4alkylR_5R_6$ is intended to imply that X4 may be absent (i.e. for C_0 -alkyl).

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved (see search report for a selection of documents) that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to compounds of formula I as defined in claim 2 wherein X1, X2 and X3 are as defined in claim 5, M2 is as defined in claim 7 and X4 is defined as in claim 10.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 26 and 27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/US 03/24846

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9926927	A	03-06-1999	AU	1531799 A	15-06-1999
			CA	2311131 A1	03-06-1999
			CN	1285820 T	28-02-2001
			EP	1037878 A2	27-09-2000
			JP	2001524468 T	04-12-2001
			NZ	505207 A	31-10-2003
			WO	9926927 A2	03-06-1999
			US	2003013715 A1	16-01-2003
			US	6429207 B1	06-08-2002
EP 0397365	A	14-11-1990	US	4914207 A	03-04-1990
			AT	102197 T	15-03-1994
			CA	2016181 A1	09-11-1990
			DE	69006907 D1	07-04-1994
			DE	69006907 T2	09-06-1994
			DK	397365 T3	24-05-1994
			EP	0397365 A1	14-11-1990
			ES	2062354 T3	16-12-1994
			FI	94639 B	30-06-1995
			IE	62936 B1	08-03-1995
			JP	1958887 C	10-08-1995
			JP	3002180 A	08-01-1991
			JP	6092404 B	16-11-1994
US 5140034	A	18-08-1992	GB	2229182 A ,B	19-09-1990
EP 0422369	A	17-04-1991	DE	3929673 A1	14-03-1991
			EP	0422369 A2	17-04-1991
			JP	3099066 A	24-04-1991
WO 0035913	A	22-06-2000	DE	19858193 A1	21-06-2000
			AU	1974100 A	03-07-2000
			WO	0035913 A1	22-06-2000
			EP	1140922 A1	10-10-2001
			JP	2002532497 T	02-10-2002
			US	2003162812 A1	28-08-2003